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(54) Title: HYDRODYNAMICALLY BALANCED ORAL DRUG DELIVERY SYSTEM

(57) Abstract: The present invention relates to a gastro-retentive oral drug delivery system structurally comprised of a highly porous matrix comprising a drug, gas generating components, sugar, release controlling agents and, optionally, spheronizing agents. The pharmaceutical composition, either in the form of pellets (multiparticulate or single unit dosage form), beads, granules or capsules, is retained in the stomach while selectively delivering the drug at the gastric levels and upper parts of small intestine over an extended period of time.

HYDRODYNAMICALLY BALANCED ORAL DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

The present invention relates to a gastro-retentive oral drug delivery system structurally comprised of a highly porous matrix comprising a drug, gas generating components, sugar, release controlling agents and, optionally, spheronizing agents. The pharmaceutical composition, either in the form of pellets (multiparticulate or single unit dosage form), beads, granules or capsules, is retained in the stomach while selectively delivering the drug at the gastric levels and upper parts of small intestine over an extended period of time.

BACKGROUND OF THE INVENTION

An orally administered drug delivery system is exposed to a wide range of highly variable conditions, such as pH, agitation intensity, gastric emptying times and composition of the gastrointestinal fluids during its transit through the digestive tract. In addition, presence of food in the tract may affect the dosage form performance. Therefore, to design an optimum oral controlled release system, it is necessary to take into account the physico-chemical and physiological environment of the gastrointestinal tract. The conventional approaches to controlled release formulations known in the art are not applicable to a variety of

drugs having an "absorption window" in the stomach or upper parts of small intestine. Furthermore, it is advantageous to retain the dosage form in the stomach thereby increasing the contact time for local activity and to achieve better therapeutic efficacy for the diseases which are confined to the upper parts of the gastrointestinal tract such as peptic and duodenal ulcers.

It is readily apparent that a sustained release formulation which slowly releases medicament over an extended period and is retained in the upper parts of gastrointestinal tract for a prolonged period would be desirable for such diseases.

The prior art discloses various approaches for therapeutic dosage forms which are designed to be retained in the upper parts of the gastro-intestinal tract and possess sustained release characteristics.

U.S. Patent No. 5,780,057 discloses a pharmaceutical tablet having a multilayer structure wherein at least one layer swells in the presence of biological aqueous fluids resulting in an increase by at least 50% of the total volume of the tablet and thereby allegedly exhibiting a high residence time in the stomach and/or in the upper portion of the gastrointestinal tract. This swellable layer, being a granular mixture of biocompatible hydrophilic polymers and highly swellable (super disintegrating) polymers, allegedly acts as a barrier and allegedly modulates the slow release of the active ingredient from

the pharmaceutical form. It is believed that the expanded dosage forms could block the pyloric sphincter or could cause unfavorable conditions following multiple dosing resulting from retention of swollen dosage units in the stomach.

U.S. Patent No. 5,651,985 discloses a composition comprising 30-90% by weight of the composition, a homogenous mixture of polymers containing lactam groups and polymers containing carboxyl groups as gel forming agents, which swells to form a gel of allegedly high mechanical and dimensional stability in the aqueous environment of the stomach. It is believed that, as the concentration of the polymers is very high, the dosage forms containing a high dose medicament would be large and inconvenient for oral administration.

U.S. Patent No. 5,007,790 discloses a sustained-release oral drug dosage form comprising a plurality of solid particles of a solid - state drug dispersed within a hydrophilic, water swellable polymer that swells on inbibition of gastric fluid to increase the particle size to a level that promotes retention in the stomach over said time period, permitting dissolution of the dispersed drug and release of the resulting solution through a leaching action. The swellable polymer also allegedly maintains its physical integrity for at least a substantial portion of the time period during which the drug is released into the stomach and thereafter, rapidly dissolves. It is well recognized by those skilled in the art that it may be difficult to obtain the desired rate of release for a drug that has a high water solubility from multiparticulate systems as

described in this patent, in which the drug first undergoes dissolution followed by release of the resulting solution by leaching action.

U.S. Patent No. 5,169,638 discloses a buoyancy controlled release powder formulation for releasing a pharmaceutical of a basic character regardless of the pH of the environment and which formulation includes upto about 45% by weight of a pH dependent polymer which is a salt of a polyuronic acid and a pH independent hydrocolloid gelling agent.

U.S. Patent No. 4,814,179 discloses a floating, sustained release therapeutic composition in form of a non-compressed tablet having a network of multitudinous air holes and passages therein and a density of less than one comprising a matrix containing 0.5 - 4% gelling agent, 10-20% oil, 50-75% therapeutic agent and water.

U.S. Patent No. 4,702,918 discloses a floating, sustained release formulation formed by heating a mixture of a gelling agent (cellulose or starch derivative) and a fat/oil which is solid at room temperature. More than mere mixing is required to impart buoyancy to the formulation, *i.e.*, melting followed by cooling is additionally required.

U.S. Patent No. 4,126,672 discloses formulations comprising one or more medicaments in combination with a hydrocolloid or mixtures of hydrocolloids so as to have a bulk density less than one and be hydrodynamically balanced when in contact with gastric fluid.

For the above-stated reasons and because they are either complicated devices and systems which are difficult to manufacture on the industrial scale or the components used therein are not so user friendly, none of the oral controlled drug delivery systems heretofore described is completely satisfactory.

Our co-pending U.S. Patent Application No. 09/152,932 filed September 14, 1998 describes a pharmaceutical composition in the form of tablets or capsules which provides a combination of spatial and temporal control of drug delivery when ingested by a patient. The pharmaceutical composition constitutes an oral controlled drug delivery system, comprising a drug, a gas generating component, a swelling agent, a viscolyzing agent and optionally a gel forming polymer. The viscolyzing agent and the gel forming polymer form a hydrated gel matrix which entraps the gas, causing the tablet or capsule to retain in the stomach or upper part of the small intestine (spatial control) and also creates a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal control).

The principle of sustained release which characterizes the formulations of the subject invention is unique in the art and no teaching has been found which recognizes the application of such a porous matrix to buoyancy and sustained release as is taught by the present invention.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a pharmaceutical composition in the form of pellets, beads, granules or capsules which constitutes a gastro-retentive oral drug delivery system that :

(a) generates a gas to form a highly porous (prefereably honeycombed) matrix with good floating characteristics and also evolves gas upon contact with gastric fluid which helps in retaining the buoyancy of the dosage form in the stomach,

(b) provides increased gastric residence and thereby extends residency of the drug delivery system in the gastrointestinal tract,

(c) delivers the drug at a controlled rate and exhibits reproducibility of release rate into aqueous media while floating in the stomach and

(d) provides, as compared to other oral controlled drug delivery systems, increased absorption of a drug that is absorbed largely from the upper parts of the gastrointestinal tract.

It is also an object of the present invention to provide a pharmaceutical composition constituting an oral controlled drug delivery system that maintains its physical integrity and dimensional

stability when in contact with gastric fluids. The system remains floating in-vitro in the simulated gastric fluid for 20-24 hours.

The present invention describes a novel therapeutic system either in the form of beads, pellets, or granules filled in a capsule (multiparticulate system) or single unit pellets and matrix capsules (monolithic system) which constitutes an orally administered buoyant delivery system capable of extended residency on gastric fluids. The delivery system is structurally composed of a highly porous matrix (preferably honeycombed) with large volume of entrapped air which makes it light and imparts good floatation characteristics.

The therapeutic system comprises a drug, a therapeutically inert oil which is solid at room temperature, a diluent, a sugar and a gas generating component.

The gas generating agents used herein are a combination of at least one thermostable and at least one thermolabile component. During the preparation of the formulation, on exposure to high temperature, the thermolabile component generates gas and aids in attaining the porous internal structure, while the thermostable component reacts with the acid in the stomach to evolve gas which helps in maintaining buoyancy of the dosage form. Thus, the combination of gas generating agents permits the therapeutic system to act as a floating matrix that extends the retention of the dosage form in the stomach and also prolongs its release in the stomach and upper

parts of the small intestine. That is, the system is not transported past the "absorption window" prior to releasing all or substantially all of the drug and maximum bioavailability is attained.

Preferably, the inventive oral controlled drug delivery system which is in the form of a multiparticulate or a monolithic system, comprises an amount ranging from a pharmaceutically acceptable amount up to 35% of a therapeutic agent, about 5% to about 50% by weight of the inert oil, about 5% to about 50% by weight of the diluent, about 5% to about 50% by weight of a sugar and about 1% to about 30% by weight of the gas generating component.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the oral pharmaceutical composition includes a drug, an inert oil, a diluent, a sugar, a combination of gas generating agents and other pharmaceutical auxiliary additives which may be used by one skilled in the art to formulate the therapeutic system. The choice of auxiliary additives and the amounts to be used are considered to be within the purview of one skilled in the art. It is to be borne in mind, however, that these conventional pharmaceutical auxiliary additives which might adversely affect the hydrodynamic balance of the formulation of the present invention are not suitable for use therein.

The gas evolved during the preparation of the formulation by the gas generating components causes the system to attain a highly

porous structure. The therapeutic agent is suspended within this highly porous, preferably honeycombed matrix.

The foregoing composition may be in the form of pellets, beads or granules filled within a capsule or a sachet (a multiparticulate drug delivery system) or matrix capsules and single unit pellets (monolithic system). The art of the producing spherical pellets by extrusion and spheronisation techniques or spheronisation using techniques based on high shear granulation or fluidised bed techniques is well known and may be used for the preparation of pellets, beads or granules in the subject invention. Single unit pellets can be produced on industrial scale using lozenge and troches cutting machines.

Drugs which are thermostable may be added into the matrix while thermolabile drugs can be loaded onto the carrier spheres (drug free pellets) using techniques of drug loading based on fluidised bed principle (equipments like Glatt) which are well known in the art. The pharmaceutical composition of the present invention may be in the form of a multiparticulate drug delivery system (upto to 4mm in size pellets, granules or beads) or a single unit form as matrix capsule or large size pellets (more than 5mm in size). The matrix capsule of the present invention may be produced by filling the powder according to the invention in a capsule made up of either gelatin, starch or hydroxypropyl methylcellulose followed with heat treatment.

There may also be incorporated into the gastro-retentive formulation of the present invention additional polymers recognized in the art of pharmaceutical compounding for their release retarding properties. These may be hydrophilic or hydrophobic in nature or may be pH dependent or independent polymers. Examples of the polymers suitable for this invention include hydroxypropyl methylcellulose, hydroxypropyl cellulose, Eudragit, ethyl cellulose, xanthan gum, and the like.

The pharmaceutical composition of the present invention may be coated with a film forming polymer to retard the release of the drug or to impart better / improved floating characteristics (which is a result of better entrapment of the gas) or to improve its organoleptic properties. Furthermore, the pharmaceutical composition may also contain bioadhesive polymers incorporated within the coating or present as a film coat on the pellets, granules, beads or capsules in order to improve its gastro-retentive properties. In another application, some highly swelling polymers may also be added to increase the size of the dosage form so as to improve its gastric retention.

The pharmaceutical composition of the subject invention, when added to simulated gastric fluids, floats on the fluid for about 20-24 hours or more. The thermostable gas generating component included therein reacts with the acid present in the media and generates gases which become entrapped within the matrix thereby enhancing the buoyancy of the formulation.

The various components of the present invention are described in more details below.

DRUG

According to the present invention, the pharmaceutical composition is in the form of pellets, beads or granules filled in a capsule, a matrix capsule or a matrix pellet, as a single unit which provides controlled release of at least one therapeutic agent or drug. The drug may be pharmacologically active itself or may be converted into the active form by biotransformation in the body. The drug can be any drug for which therapy would be improved as a result of controlled drug delivery and increased gastric retention.

The medicament or combination of medicaments which are amenable to controlled release therapy utilising the novel formulations of the present invention include any of those suitable for oral administration. The present invention is not to be construed as being limited to any particular medicament or class of medicaments.

The gastro-retentive formulations of the subject invention are particularly amenable to the administration of medicaments which are predominantly absorbed through the stomach or upper portion of the intestines, drugs having pH dependent solubility i.e. more soluble in the gastric pH as compared to the intestinal pH, drugs having stomach as a site of action which includes H-2 receptor antagonists, antacids,

antimuscarinic agents , proton pump inhibitors, drugs active against *H. pylori*, cytoprotective agents, and the like.

Illustrative examples of drugs that are absorbed predominantly from the upper parts of gastrointestinal tract include ciprofloxacin, cyclosporin, furosemide, metoprolol, oxprenolol, baclofen, allopurinol, sumatriptan, benazepril, enalapril, quinapril, moexipril, indolapril, olindapril, retinapril, spirapril, cilazeprilat, lisinopril, imidapril, benazeprilat, cilazapril, captopril, delapril, tosinopril, libenzapril, pentopril, perindopril, altiopril, quinaprilat, ramipril, spiraprilat, zofenopril, and the like; all of which are suitable for use in the present invention.

Drugs having the stomach as site of action include H-2 receptor antagonists such as ranitidine, famotidine, nizatidine, bifentidine, erbrotidine, nifentidine, roxatidine and cimetidine, and the like; proton pump inhibitors like omeprazole, lansoprazole, pentoprazole, and the like; antacids like magnesium carbonate, aluminium hydoxide, magnesium oxide and simethicone, and the like; cytoprotectives such as sucralphate, carbenoxolone sodium and misoprostol, and the like; antimuscarinic agents like pirenzepine, telenzepine and propanthelene bromide, and the like; drugs active against *H.Pylori* like bismuth salts such as bismuth subsalicylate, tripotassium dicitratobismuthate, ranitidine bismuth citrate, and the like; antibiotics for example clarithromycin, amoxycillin, and the like; all of which are suitable for use in the present invention.

Other medicaments that are suitable for this invention are drugs having solubility in acidic pH or ones having specific absorption sites in the stomach or upper parts of the intestine and those that are subjected to gastro-intestinal first pass metabolism (as in some reports stomach absorption is known to bypass gastrointestinal first pass metabolism) include antihypertensive agents like verapamil, nifedipine, propranolol, nimodipine, nicardipine, amlodipine, prazosin, ketanserin, guanabenz acetate, hydralazide, methyldopa, levodopa, carbidopa; antivirals like acyclovir, inosine, pranobex, zidovudine (AZT), tribavirin, vidarabine; lipid lowering agents like simvastatin, pravastatin, atorvastatin and lovastatin; antipsychotic agents like selegiline; sedatives like midazolam; all of which are suitable for use in the present invention.

The drug itself or its pharmacologically active salt or ester can be used in the present invention. Moreover combination of drugs that are typically administered together may be included as the drug component. The amount of drug is that which is typically administered for a given period of time. Accordingly the drug may be present in an amount ranging from a pharmaceutically acceptable amount up to 35% by weight of the total weight of the composition.

OIL

According to the present invention, the pharmaceutical composition contains a therapeutically inert oil which is solid at room

temperature but softens at higher temperatures, that is, around 50-80°C. The oil forms an integral part of the highly porous, preferably honeycombed structure of the present invention and also acts as a release retarding agent . The oil is preferably a fully hydrogenated or partially hydrogenated vegetable fat or oil. Examples of oils that may be used in the present invention include partially or fully hydrogenated cottonseed oil, coconut oil, soyabean oil, palm oil, kernel oil, peanut oil, sunflower oil, and the like. The oils preferred for the present invention are mentioned in the United States Pharmacopoeia as type 1 hydrogenated vegetable oils. These oils may be used alone or in combination with other oils having the same characteristics.

The oil may be present in an amount from about 5% to about 50 % preferably about 5% to about 45 % and more preferably about 5% to about 35% by weight of the total weight of the composition.

SUGARS

According to the present invention, the pharmaceutical composition contains sugars which provide low density airy structure of the desired texture to the matrix. The examples of sugars preferred for the present invention include sucrose, glucose syrup, corn syrup, crystalline fructose, fructose, lactose, dextrose, galactose, maltodextrin, maltose, and the like, sugar alcohols like sorbitol, mannitol, maltol, maltitol, xylitol, lactitol. In more preferred embodiments of the subject invention the sugar is glucose syrup either

in the dried form or as a liquid. Glucose syrups having dextrose equivalents ranging from 20% to greater than 73% are suitable for this invention. Sugars may be used alone or in the combination with other similar sugars to achieve suitable matrix properties. In one preferred embodiment, sugar which is available under the brand name Glucidex (Roquette, UK) may be used.

The sugar may be present in an amount from about 5% to about 50% preferably from about 5% to about 45% and more preferably from about 5% to about 35% by weight of the total weight of the composition.

DILUENTS

According to the present invention, the pharmaceutical composition comprises a diluent which is stable to drying/treatment temperatures and forms an essential part of the highly porous, preferably honeycombed structure. The diluent that may be used in the present invention, belongs to the class of excipients recognised in the art of pharmaceutical compounding. In preferred embodiments of the present invention, the diluent is starch. Examples of starches that may be used in the present invention include maize starch, rice starch, potato starch or corn starch. Examples of other diluents include dibasic calcium phosphate, calcium sulfate, powdered cellulose, microcrystalline cellulose, and the like.

The diluent may be present in an amount from about 5% to about 50% by weight of the total weight of the composition, preferably from about 5% to about 40% and more preferably from about 5% to about 35% by weight of the total weight of the composition.

GAS GENERATING COMPONENTS

According to the present invention, the pharmaceutical composition contains a combination of thermolabile and thermostable gas generating agents which aid in the formation of the highly porous, preferably honeycombed structure and enhances the buoyancy of the formulation. As the name suggests, the thermolabile gas generating component produces gas upon exposure to high temperature during drying/treatment phase while the thermostable component does not dissociate upon heating and produce gas upon contact with gastric fluid. Examples of gas generating components that may be used in the present invention include carbonates such as calcium carbonate or sodium glycine carbonate, bicarbonates such as sodium hydrogen carbonate or potassium hydrogen carbonate , sulfites such as sodium sulfite, sodium bisulfite or sodium metabisulfite and the like. The thermostable gas generating component interacts with an acid source triggered by contact with water or simply with gastric acid to generate carbon dioxide or sulphur dioxide that gets entrapped within the highly porous, preferably honeycombed matrix of the composition and improves its floating characteristics.

In those embodiments of the present invention, where the pharmaceutical composition is in the form of a capsule, gas generating components may be used alone or in combination with an acid source as a couple. The acid source may be one or more of edible organic acids , a salt of an edible organic acid, or mixtures thereof. Examples of organic acids that may be used as the acid source in the present invention include citric acid or its salts such as sodium citrate or calcium citrate, malic acid , tartaric acid , succinic acid, fumaric acid , maleic acid or their salts, and the like. The organic acid salts which may be used as the acid source in the present invention include, for example, a mono-alkali salt of an organic acid having more than one carboxylic acid functional group, a bialkali metal salt of an organic acid having more than two carboxylic acid functional groups, and the like.

The gas generating agents may be present in amounts from about 1% to about 40 % preferably from about 1% to about 35 % and more preferably from about 1% to about 30% by weight of the total weight of the composition.

OTHER EXCIPIENTS

Optionally, there may also be incorporated into the buoyant formulation of the present invention, other conventional pharmaceutical excipients known in the art of formulation development such as spheronising agents, binding agents and release retarding agents.

According to the present invention the pharmaceutical composition is prepared either in the form of pellets, granules, beads or as matrix capsules. The pellet /beads can be prepared using the commonly known techniques for extrusion and spheronisation and also other granulation techniques. Spheronising agents are added to the composition to get uniform spherical granules or pellets. Commonly used spheronisation aids are microcrystalline cellulose (Avicel PH 101 of FMC Corpn. and Emcocel 50M of Mendell) , mixture of microcrystalline cellulose and sodium carboxymethyl cellulose (Avicel RC 591 of FMC Corpn.)

The spheronising agent may be present in amounts from about 5% to about 30% preferably from about 5% to about 20% and more preferably from about 5% to about 15 % by weight of the final weight of the compostion.

The pharmaceutical composition in the form of beads may also include a binder to provide cohesiveness to the powder mass. The binders commonly known to the pharmaceutical art may be used in the present invention. Examples of the binders are pregelatinised starch, polyvinylpyrollidone, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, starch paste, gelatin, xanthan gum ,acacia, guar gum, and the like.

The binder may be present in amounts from about 0.1% to about 15% , preferably about 0.1% to about 12% and more preferably

about 0.1% to about 10% by weight of the final weight of the composition.

The pharmaceutical composition according to the present invention may also contain some polymers in addition to the hydrogenated vegetable oils to retard the release of the drug. These polymers may be present within the matrix structure of the pellets or capsules or may be coated onto the composition or may be added in capsule presentations of the present invention in the powder form. The polymers obtained as aqueous dispersions may replace water as granulating agent in the pellet preparations. Solid polymers may be added directly into the powder blend.

The polymers used may be of the hydrophilic or the hydrophobic type or pH dependent or pH independent in nature. Examples of the polymers suitable for this invention include the polymers well known in the pharmaceutical art for their release retarding properties, for example, cellulose ethers as hydroxypropyl celluloses of different grades, hydroxyethylcellulose, methylcellulose, hydroxypropyl ethylcellulose; acrylic polymers which are obtained as aqueous dispersions like Eudragit NE30D, Eudragit RS30D, Eudragit RL30D, Eurdagit L30D or available as powders such as Eudragit RSPO , Eudragit RLPO, Eudragit L10055 (all supplied by Rohm Pharma, Germany), Ethyl cellulose as aqueous dispersion or in powder form. Examples of highly swellable polymers that may be used in the present

invention include hydroxypropyl methylcelluloses of different grades, xanthan gums, sodium alginate, and the like.

The release retarding polymers may also be selected from the class of natural gums as karaya gum, locustbean gum, guar gum, gellan gum, and the like.

The release retarding agents may be present from about 1% to about 25%, preferably from about 1% to about 20 % or more preferably from about 1% to about 15% by weight of the total weight of the composition.

According to the present invention the capsule shell may be of a hard gelatin or a soft gelatin type. Furthermore, capsules made of starch or hydroxypropyl methylcellulose may also be used.

The present invention is illustrated by, but is by no means limited to, the following examples:

EXAMPLE 1

This example illustrates the present invention in the form of pellets in which Eudragit NE 30 D has been used as a release retarding polymer in conjunction with hydrogenated vegetable oil within the matrix. The active ingredient is Diltiazem Hydrochloride:

TABLE 1

INGREDIENTS	%W/W
Diltiazem Hydrochloride	20.40
Hydrogenated cottonseed oil (Lubritab)	16.48
Starch (Maize)	22.09
Dried Glucose Syrup (Glucidex 40*)	16.48
Pregelatinised starch (Starch 1500)	1.32
Microcrystalline cellulose (Avicel PH 101)	9.88
Ammonium Bicarbonate	2.75
Calcium Carbonate	4.95
Eudragit NE 30 D	5.65 (as solids)
	100.00

*Dextrose equivalent – 40%

Diltiazem Hydrochloride, Hydrogenated cottonseed oil, Starch, Glucose syrup, Pregelatinised starch, Microcrystalline cellulose, Ammonium bicarbonate and Calcium carbonate were sieved through a sieve (British Standard Sieve (BSS) 44; 355 μm) and mixed. The blend was granulated with Eudragit NE 30 D dispersion and extruded through an extruder (GA 65, Alexenderwerk) fitted with 3.5 mm roller. The extrudates were spheronised in a spheronizer (Caleva 120mm) for 20 min. The pellets thus obtained were dried in an oven maintained at 120°C for 25 min. The pellets were allowed to cool down to room temperature.

The pellets were tested for their floating properties and drug release in 900ml of 0.1N HCl using USP Apparatus 2 (paddle type) at 50 rpm. The pellets equivalent to 30 mg of Diltiazem Hydrochloride were added to the dissolution vessel.

At periodic time intervals the visual observations were made to see the sinking pellets, if any. It was noted that all the pellets remained floating until 21 hours. The samples of the dissolution media was periodically withdrawn and analysed for Diltiazem content spectrophotometrically. The results are shown in Table 2.

TABLE 2

Time (hrs)	cumulative % release
1	53.95
2	67.95
3	76.91
4	85.00
5	88.42

EXAMPLE 2

This example illustrates the present invention in the form of matrix capsules using Propranolol Hydrochloride as an active agent. The pharmaceutical composition is illustrated in Table 3.

TABLE 3

INGREDIENTS	%W/W
Propranolol Hydrochloride	20.00
Starch (Maize)	14.28
Hydrogenated cottonseed oil (Lubritab)	22.86
Dried Glucose Syrup (Glucidex 40*)	28.58
Ammonium Bicarbonate	7.14
Calcium carbonate	7.14
	100.00

Propranolol hydrochloride, Starch, Hydrogenated vegetable oil, Glucose syrup, Ammonium bicarbonate and Calcium carbonate were together sieved through a sieve (British Standard Sieve (BSS) 44, 355µm) and mixed. The blend was manually filled in size-2 gelatin capsules. The average fill weight of the composition was 320mg. The filled capsules were kept in an oven maintained at 110º C for 2.5 minutes, following which they were cooled to room temperature.

The capsules were tested for their floating properties and drug release in a 900ml of 0.1N HCl using USP Apparatus 2 (paddle) at 50 rpm. At periodic time intervals the visual observations were carried out to see the floating or sinking of the capsules. It was noted that the capsules remained floating till 20 hours. The samples of the media were periodically withdrawn and tested for propranolol content spectrophotometrically. The dissolution results are recorded in Table 4.

TABLE 4

TIME (HOURS)	CUMULATIVE % RELEASE
1	12.41
2	21.02
4	34.06
20	81.71

EXAMPLE 3

This example illustrates the present invention in the form of pellets which do not contain any drug. These pellets may be used as carriers for drugs which may not be loaded within the matrix. The pharmaceutical composition is given in Table 5.

TABLE 5

INGREDIENTS	%W/W
Hydrogenated cottonseed oil (Lubritab)	10.86
Starch (Maize)	32.61
Dried Glucose Syrup (Glucidex 40 *)	32.61
Pregelatinised starch (Starch 1500)	0.87
Microcrystalline celluose (Avicel PH 101)	8.70
Ammonium bicarbonate	4.35
Calcium carbonate	6.52
Eudragit NE 30 D	3.48 (as solids)
	100.00

- Dextrose equivalent -40%

Lubritab, Starch maize, Glucose syrup, Pregelatinised starch, Microcrystalline cellulose, Ammonium bicarbonate and Calcium carbonate were sieved through 355 µm mesh (British Standard Sieve (BSS) 44) and mixed. The blend was granulated with the Eudragit dispersion and extruded through an extruder (GA65, Alexenderwerk) fitted with 3.5 mm roller. The extrudes were spheronised in a 120mm spheronizer (Caleva) for 60 min. The pellets thus obtained were dried at 100º C for 15 min. following which they were allowed to cool to room temperature.

The pellets were tested for their floating properties using 900ml of 0.1 N HCl , in a dissolution USP apparatus 2 with paddle speed at 50 rpm . At periodic time intervals visual observations were made for the floating properties of the formulation. It was noted that the pellets remained buoyant for 20 hours.

EXAMPLE 4

This example illustrates single unit pellets (6 to 8 mm in diameter) which may be used as single unit dosage forms, containing Diltiazem Hydrochloride as an active ingredient.

The pharmaceutical composition is illustrated in Table 6.

TABLE 6

INGREDIENTS	% W/W
Diltiazem Hydrochloride	22.37
Hydrogenated cottonseed oil (Lubritab)	10.28
Starch (Maize)	30.30
Dried Glucose Syrup (Glucidex 40*)	12.12
Pregelatinised starch (Starch 1500)	6.04
Microcrystalline cellulose (Emcocel 50M)	9.62
Ammonium bicarbonate	3.87
Calcium carbonate	5.40
	100.00

*Dextrose equivalent --40%

Diltiazem Hydrochloride , Hydrogenated cottonseed oil, Starch, Glucose syrup, Pregelatinised starch, Microcrystalline cellulose, Ammonium bicarbonate and Calcium carbonate were sieved through 355 µm mesh (British Standard Sieve (BSS) 44) and mixed. The blend was granulated with water to get a dough like consistency . The dough was rolled into cylindrical shape and small pieces weighing for 30 mg of Diltiazem Hydrochloride were cut out and manually rolled into spherical shape.

The pellets were dried in an oven maintained at 120°C for 10 min. following which they were allowed to cool down to room

temperature. The pellets were characterised for floating and drug release as described in Example – 1. The pellets were found to float on the media for 20 hours. The dissolution results are recorded in Table 7

TABLE 7

TIME (HOURS)	CUMULATIVE % RELEASE
1	36.29
2	52.39
3	67.06
4	75.14
5	82.97
6	86.72
7	87.74

EXAMPLE 5

This example illustrates the capsule type of dosage form in which an organic acid is used in combination with the gas generating agents as a couple. The pharmaceutical composition is given in Table 8.

TABLE 8

INGREDIENTS	%W/W
Propranolol Hydrochloride	21.46
Starch (Maize)	10.52
Dried Glucose Syrup (Glucidex 40)	22.45
Hydrogenated cottonseed oil (Lubritab)	28.06
Citric Acid, anhydrous	3.51
Ammonium Bicarbonate	7.00
Calcium carbonate	7.00

All the ingredients were sieved through 355 μm mesh (British Standard Sieve (BSS), 44) and mixed. The blend was filled manually in size-2 gelatin capsules . The average fill weight was 320 mg. The capsules were given heat treatment at 110°C for 2.5 minutes, following which they were cooled to room temperature.

The capsules were tested for in-vitro dissolution and floating characteristics as described in Example 2. The capsules remained floating on the dissolution media throughout the dissolution test of 24 hours . Dissolution results are recorded in Table 9.

TABLE 9

TIME (HOURS) RELEASE	CUMULATIVE %
1	22.77
2	33.46
4	49.07
6	60.18
10	73.24
24	86.39

EXAMPLE 6

The present example illustrates the capsule type of dosage form made according to the present invention containing a polymer within the matrix (xanthan gum) together with the gas generating couple consisting of an organic acid and the gas generating agents. The

blend was filled in size-2 gelatin and size-0 HPMC capsules. Table 10 illustrates the pharmaceutical composition.

TABLE 10

INGREDIENTS	%W/W
Propranolol Hydrochloride	19.41
Starch (Maize)	9.52
Dried Glucose Syrup (Glucidex 40)	20.30
Hydrogenated cottonseed oil (Lubritab)	25.38
Citric acid, anhydrous	3.17
Xanthan Gum	9.52
Ammonium Bicarbonate	6.35
Calcium carbonate	6.35

All the ingredients were weighed and passed through 355 μm mesh (British Standard Sieve (BSS), 44) and mixed. The blend was filled manually in size-2 gelatin capsules (average fill weight 325mg) and size-0. Hydroxypropyl methylcelluiose capsules (average fill weight 520mg). The capsules were kept in an oven maintained at 110º C for 2.5 minutes, following which they were cooled to room temperature.

The capsules were tested for floating characteristics and dissolution profile as described in Example - 2. The capsules remained

floating on the top of the media for 24 hours. Dissolution results are recorded in Table 11.

TABLE 11

TIME (HOURS)	CUMULATIVE % RELEASE	
	SIZE 2	SIZE 0
1	19.02	6.60
2	32.15	19.52
4	57.54	50.24
6	73.42	70.59
10	87.80	88.09
24	92.41	95.08

While the invention has been described by reference to specific examples, this was for the purpose of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are considered to be within the scope of this invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition which constitutes an oral drug delivery system for prolonged gastric retention having a highly porous matrix, comprising:

a therapeutic agent, a therapeutically acceptable inert oil, a sugar, a diluent, a gas generating component which is a combination of at least one thermostable and at least one thermolabile component, and optionally pharmaceutically acceptable auxiliary components wherein the pharmaceutical composition substantially maintains its hydrodynamic balance and physical integrity for the time period during which the drug is released into the stomach.

2. A pharmaceutical composition according to claim 1 wherein the active compound comprises at least one compound selected from the therapeutic category of antiulcer, analgesic, antihypertensive, antibiotic, antipsychotic, anticancer, antimuscarinic, diuretic, antimigraine, antiviral, anti-inflammatory, sedatives, antidiabetic, antidepressant, anti-histaminic, antiparasitic, antiepileptic and lipid lowering drugs.

3. A pharmaceutical composition according to claim 1 wherein the active compound is selected from the group comprising of enalapril, captopril, benazepril, lisinopril, ranitidine, famotidine, ranitidine bismuth citrate, diltiazem, propranolol, verapamil,

nifedipine, acyclovir, ciprofloxacin, simvastatin, atorvastatin, lovastatin, selegiline, midazolam, fluoxetine, acarbose, buspirone, nimesulide, captopril, nabumetone, glimepiride, glipizide, etodolac and nefazodone.

4. A pharmaceutical composition according to claim 1 wherein the drug is present in an amount ranging from a pharmaceutically acceptable amount up to 35% by weight of said composition.

5. A pharmaceutical composition according to claim 1 wherein the inert oil comprises a partially or fully hydrogenated vegetable oil.

6. A pharmaceutical composition according to claim 1 wherein the inert oil is selected from the group consisting of a partially hydrogenated cottonseed oil, a fully hydrogenated cottonseed oil, castor oil, coconut oil, kernel oil, palm oil, soybean oil, and peanut oil.

7. A pharmaceutical composition according to claim 1 wherein the inert oil comprises about 5% to about 45% by weight of said composition.

8. A pharmaceutical composition according to claim 1 wherein the inert oil comprises about 5% to about 35% by weight of said composition.

9. A pharmaceutical composition according to claim 1 wherein sugar is selected from the group consisting of sucrose, glucose syrup, corn syrup, fructose, lactose, dextrose, galactose, maltose, maltodextrin, sorbitol, mannitol, maltol, maltitol, xylitol and lactitol.

10. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 5% to about 50% by weight of said composition.

11. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 5% to about 45% by weight of said composition.

12. A pharmaceutical composition according to claim 1 wherein the sugar comprises about 5% to about 35% by weight of said composition.

13. A pharmaceutical composition according to claim 1 wherein the diluent is selected from the group consisting of starch, celluiose derivatives, dibasic calcium phosphate and calcium sulfate.

14. A pharmaceutical composition according to claim 1 wherein the diluent is starch.

15. A pharmaceutical composition according to claim 1 wherein the diluent comprises about 5% to about 50% by weight of said composition.

16. A pharmaceutical composition according to claim 1 wherein the diluent comprises about 5% to about 35 % by weight of said composition.

17. A pharmaceutical composition according to claim 1 wherein the gas generating component is a sulfite, a carbonate or a bicarbonate salt.

18. A pharmaceutical composition according to claim 1 wherein the gas generating component is selected from the group consisting of ammonium bicarbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium glycine carbonate, sodium sulfite, sodium bisulfite and sodium metabisulfite.

19. A pharmaceutical composition according to claim 1 wherein the gas generating component is a gas couple comprising a gas generating salt and an edible organic acid or a salt of an edible organic acid.

20. A pharmaceutical composition according to claim 19 wherein the edible organic acid is selected from the group consisting of citric acid, ascorbic acid, tartaric acid, succinic acid, fumaric acid,

malic acid, maleic acid, glycine, sarcosine, alanine, taurine and glutamic acid.

21. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 40% by weight of said composition.

22. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 35 % by weight of said composition.

23. A pharmaceutical composition according to claim 1 wherein the gas generating component comprises about 1% to about 30% by weight of said composition.

24. A pharmaceutical composition according to claim 1 wherein the pharmaceutical auxilary substance is selected from the group comprising of binding agents, spheronising agents and release retarding agents.

25. A pharmaceutical composition according to claim 24 wherein the binding agent is selected from the group consisting of pregelatinised starch, polyvinylpyrollidone, gelatin, hydroxy-propyl methylcellulose, sodium carboxymethyl cellulose and natural gums.

26. A pharmaceutical composition according to claim 24 wherein the binding agent comprises about 0.1% to about 15% by weight of said composition.

27. A pharmaceutical composition according to claim 24 wherein the binding agent comprises about 0.1% to about 10% by weight of said composition.

28. A pharmaceutical composition according to claim 24 wherein the spheronising agent is microcrystalline cellulose or a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose.

29. A pharmaceutical composition according to claim 24 wherein the spheronising agent comprises about 5% to about 30% by weight of said composition.

30. A pharmaceutical composition according to claim 24 wherein the spheronising agent comprises about 5% to about 15% by weight of said composition.

31. A pharmaceutical composition according to claim 24 wherein the release retarding agent is either incorporated into the matrix or coated onto said composition.

32. A pharmaceutical composition according to claim 24 wherein the release retarding agent is selected from the group consisting of cellulose ethers, acrylic polymers and natural gums.

33. A pharmaceutical composition according to claim 24 wherein the release retarding agent comprises about 1% to about 25% by weight of said composition.

34. A pharmaceutical composition according to claim 24 wherein the release retarding agent comprises about 1% to about 15% by weight of said composition.

35. A pharmaceutical composition according to claim 1 being formed into a physical form selected from the group consisting of multiple unit pellets, single unit pellets, beads, granules, soft gelatin shell capsules, and hard gelatin shell capsules.

36. A pharmaceutical composition according to claim 35 wherein the capsule shell is made of gelatin, hydroxypropyl methylcellulose or starch.

37. A pharmaceutical composition according to claim 1 further comprising a bioadhesive polymer.

38. A pharmaceutical composition according to claim 1 further comprising a highly swellable polymer.

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/IB 99/01386

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 13760 A (GERGELY GERHARD) 22 July 1993 (1993-07-22) claims 1-4,7,8 examples 4,5	1,2, 4-27, 29-38
A	GB 2 283 172 A (RP SCHERER) 3 May 1995 (1995-05-03) claims 1-3,8,9,11,15 page 3, line 20 - line 25 page 4, line 21 - line 32 page 5, line 1 - line 8 page 5, line 35 -page 6, line 4 page 8, line 4 - line 7	1-38

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2000	06/04/2000

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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